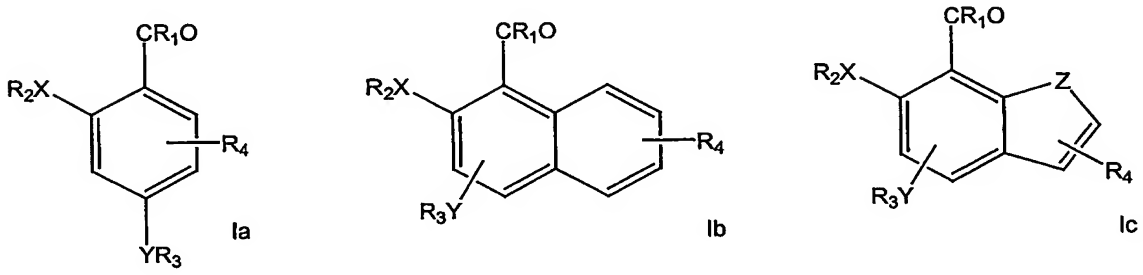
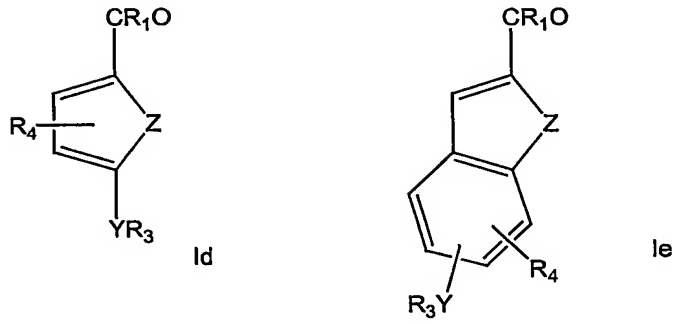
CLAIMS

1. A positive charge-balanced linker according to general formulae (Ia to Ie):





General formulae (I)

wherein:

X = O or S;

Y is O, S or CH_2, CHR, CRR, where R is C_{1-7} alkyl;

Z is O or S;

R_1 is H or C_{1-7} alkyl;

R_2 is H or C_{1-7} alkyl;

R_4 is H or C_{1-7} alkyl at any vacant position on the aromatic ring;

R_3 is C_{1-7} alkyl-L_1-R_5-L_2- R_6-COOH, C_{3-10} cycloalkyl-L_1-R_5-L_2- R_6-COOH or Ar-C_{0-7} alkyl-L_1-R_5-L_2- R_6-COOH;

each of L_1 and L_2 is absent or a suitable linker such as an amide CONH; or an ether -O-, or a thioether -S- or a sulphone -SO_2-;

R_5 is C_{1-7} alkyl, C_{3-10} cycloalkyl or Ar-C_{0-7} alkyl each of which is substituted with either NR_8R_9, where the nitrogen atom is capable of being protonated in solution to give $N^+HR_8R_9$; or a quaternary nitrogen atom $N^+R_8R_9R_{10}$, such that R_5 contains a positive charge;

each of R_8, R_9 and R_{10} is independently C_{1-7} alkyl, C_{3-10} cycloalkyl or Ar-C_{0-7} alkyl, or any two or more of R_8, R_9 and R_{10} together form an alicyclic or arylalicyclic ring system;

R_6 is C_{1-7} alkyl, C_{3-10} cycloalkyl or Ar-C_{0-7} alkyl;

or a salt, hydrate, solvate, complex or prodrug thereof.

2. A compound as claimed in claim 1 wherein, independently or in any combination:

X is oxygen;

Y is oxygen;

R_1 is hydrogen, methyl or ethyl;

R_2 is hydrogen or C_{1-4} alkyl;

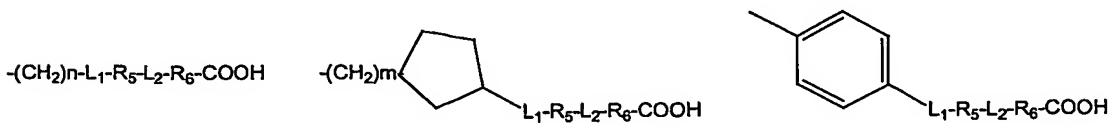
L_1 is an amide (CONH); and

L_2 is an amide (CONH).

3. A compound as claimed in claim 2, wherein R_1 is hydrogen.

4. A compound as claimed in claim 2 or claim 3, wherein R_2 is hydrogen or methyl.

5. A compound as claimed in any one of claims 1 to 3 wherein R_3 comprises



wherein n = 2-6;
m = 1-3.

6. A compound as claimed in any one of claims 1 to 5, wherein NHR_5CO (where the NH is part of the L_1 moiety and the CO is part of the L_2 moiety) comprises a simple amino acid residue that contains a side-chain protonatable amine functionality.

7. A compound as claimed in claim 6 wherein NHR_5CO is represented by the formula:

$$-NH-CH[(CH_2)_pN^+R_8R_9R_{10}]CO-$$

wherein p is 1 to 5 and R_8, R_9 and R_{10} are as defined above.

8. A compound as claimed in claim 7, wherein p is 1 to 4.

9. A compound as claimed in any one of claims 1 to 8 wherein R_8, R_9 and R_{10} groups are each independently C_{1-4} alkyl.

10. A compound as claimed in any one of claims 1 to 8 wherein R_6 combines with an NH group derived from the L_2 moiety and the terminal COOH to form an amino acid residue of the formula:

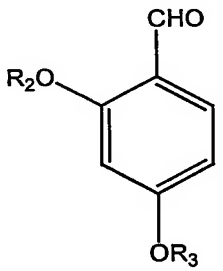
$$-NH-(CH_2)_q-A_s-(CH_2)_rCOOH;$$

where q and r are each 0 to 3, provided that both q and r are not both 0;
s is 0 or 1; and
A is a 5-10 membered stable monocyclic or bicyclic aromatic ring or a 3-6 membered carbocyclic or alicyclic ring.

11. A compound as claimed in claim 10 wherein r and s are 0 and q is 1 or 2.

12. A compound as claimed in any one of claims 1 to 11, which is a compound of general formula (Ia) as defined in claim 1.

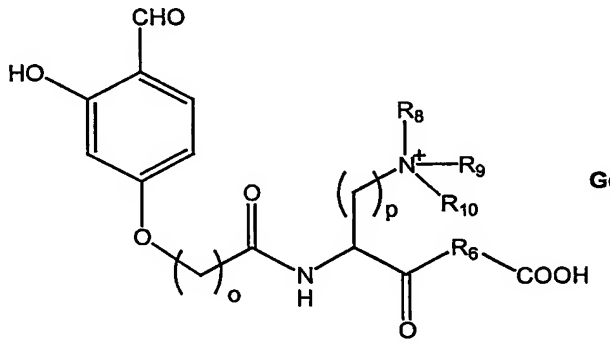
13. A compound as claimed in claim 12, which is a compound of general formula (II):



General formula (II),

which is a compound of general formula (Ia) in which X and Y are O, R_1 is H and R_2 and R_3 are as defined in claim 1.

14. A compound as claimed in claim 13, which is a compound of general formula (III):



General formula (III)

wherein:

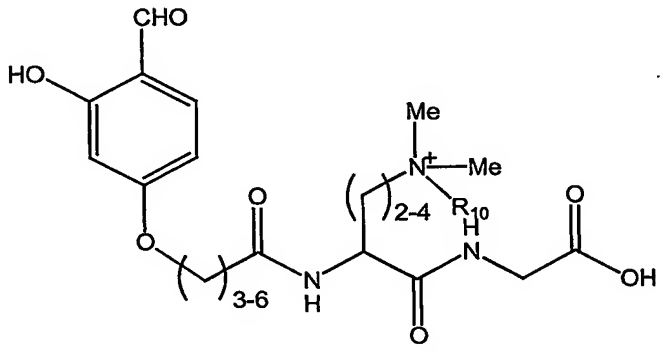
o is an integer from 2-6;

p is an integer from 1 to 5; and

R_6, R_8, R_9 and R_{10} are as defined in claim 1.

15. A compound as claimed in claim 14, wherein p is an integer from 1 to 4.

16. A compound as claimed in claim 15, which is a compound of general formula (IV):



General formula (IV)

wherein R_{10} = H or methyl.

17. A process for the preparation of a compound of general formula (I) in which L_1 and L_2 are CONH, the process comprising:

(i) reacting a compound of general formula V:

$$H_2N\text{-}R_6\text{-}COOH \qquad (V)$$

wherein R_6 is as defined for general formula (I) in claim 1; and

wherein the compound of general formula (V) is bound at its C-terminus to a solid support;

with a compound of general formula (VI):

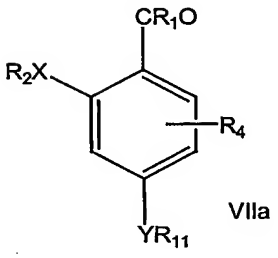
W-NH-R_5-COOH (VI)

wherein:

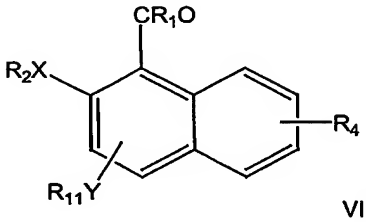
R_5 is as defined for general formula (I) in claim 1; and

W is a protecting group.

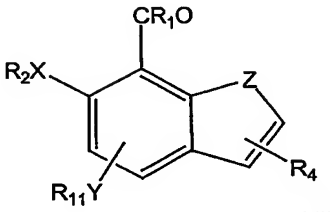
(ii) removal of the protecting group W and reaction with a compound of general formula (VII):



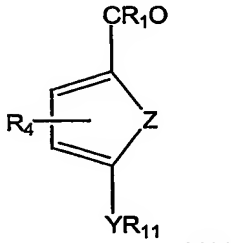
VIIa



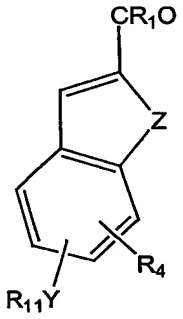
VIIb



VIIc



VIId



VIIe

General formulae (VII)

wherein

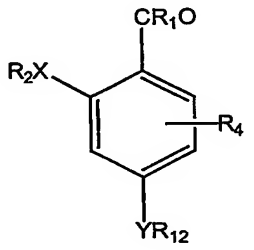
X, Y, Z, R_1, R_2 and R_4 are as defined for general formula (I) in claim 1; and

R_{11} is C_{1-7} alkyl-COOH, C_{3-10} cycloalkyl-COOH or Ar-C_{0-7} alkyl-COOH; and

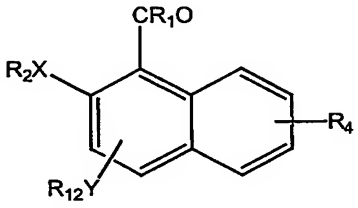
(iii) removal of the product from the solid support.

18. A process as claimed in claim 17 wherein, in the compound of general formula (VI), W is a urethane protecting group.

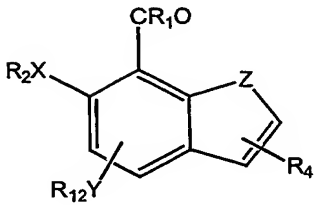
19. A compound of general formula (XIV):



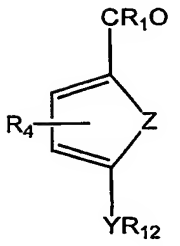
XIVa



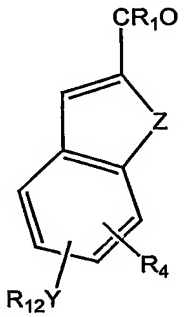
XIVb



XIVc



XIVd



XIVe

General formulae (XIV)

wherein

X, Y, Z, R_1, R_2 and R_4 are as defined for general formula (I); and

R_{12} is C_{1-7} alkyl-L_1-R_5-L_2-R_6CONHQ, C_{3-10} cycloalkyl-L_1-R_5-L_2-R_6CONHQ or Ar-C_{0-7} alkyl-L_1-R_5-L_2-R_6CONH-Q;

wherein L_1, L_2, R_5 and R_6 are as defined in general formula (I);

Q is a residue which is part of a carrier and which either contains groups from which the "NH" moiety in R_{12} is derived or has been derivatised so as to include such groups;

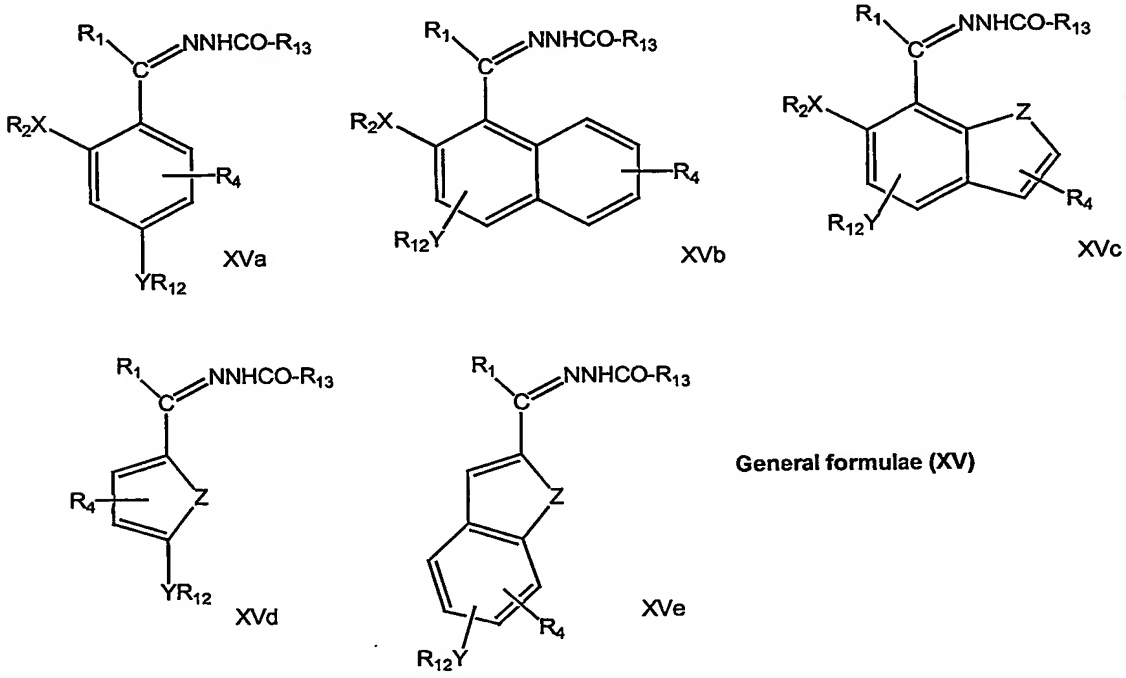
wherein the carrier may contain multiple Q residues that already have 0,1,2,...*nn* linker molecules of general formula (I) attached;

wherein the integer *nn* is the total number of Q residues available for attachment of a linker molecule to a specific carrier, where *nn* will be different for each specific carrier.

20. A compound as claimed in claim 19 wherein Q is part of a proteinaceous molecule, a polysaccharide, cellulose beads, a polymeric amino acid, a polymer, which may be a copolymer, an inactive virus particle or attenuated bacteria.

21. A process for the preparation of a compound as claimed in claim 19 or claim 20, the process comprising reacting a compound of general formula (I) as defined above with a carrier.

22. A compound of general formula (XV):



General formulae (XV)

wherein X, Y, Z, R_1, R_2 and R_4 are as defined for general formula (I);

R_{12} is as defined in general formula (XIV) as claimed in claim 19;

R_{13} is $(CH_2)_tCONH$-E, CONH-E or G;

t is an integer from 1 to 5;

E is derived from an active moiety which either contains an amino group or has been derivatised to do so; and NHE is derived from the amino group of the active moiety;

G is an active moiety bound to the carbonylhydrazide through a carbon atom

23. A compound as claimed in claim 22 which comprises E or G groups derived from two or more active moieties.

24. A process for the preparation of a compound of general formula (XV) as defined in claim 22, the process comprising reacting a compound of general formula (XIV) as defined above with a compound of general formula (XVIa), (XVIb) or (XVIc):

$E\text{-}NH\text{-}CO\text{-}(CH_2)_tCONHNH_2$	(XVIa)
$E\text{-}NH\text{-}CO\text{-}NHNH_2$	(XVIb)
$G\text{-}CO\text{-}NHNH_2$	(XVIc)

where E, G and t are as defined in claim 22.

25. A compound as claimed in claim 22 or claim 23 which is soluble in aqueous solution.

26. A compound as claimed in claim 25 wherein E or G is derived from an epitope or mimotope.

27. A compound as claimed in claim 26 wherein the epitope is a fragment, for example an antigenic determinant, derived from a protein or peptide molecule or a variant thereof.

28. A compound as claimed in claim 26 or claim 27 wherein the epitope is a B cell or T cell epitope.

29. A compound as claimed in any one of claims 25 to 28 which includes another active moiety selected from an immunomodulating compound such as a lipid, adjuvant, an immunostimulating DNA sequence or cytokine attached to the carrier protein.

30. A method for raising specific antibodies against the epitope or mimotope, the method comprising immunising a subject with a compound as claimed in any one of claims 26 to 29.

31. A compound as claimed in any one of claims 26 to 29 for immunising a subject in order to raise antibodies to an epitope or mimotope.

32. The use of a compound as claimed in any one of claims 26 to 29 in the preparation of an agent for raising antibodies against an epitope or mimotope.

33. A compound as claimed in any one of claims 26 to 29 for use as a vaccine.

34. A pharmaceutical composition comprising compound as claimed in any one of claims 26 to 29 together with a pharmaceutically acceptable excipient.

35. A pharmaceutical composition as claimed in claim 34 which is a vaccine composition and which further comprises a pharmaceutically acceptable adjuvant.

36. A non-destructive method of quantifying the extent and/or rate of reaction of a protein with a linker of general formula (I) as defined in claim 1 in which R_2 is H and X is O, the method comprising either:

a) measuring the intensity of the absorbance spectrum at a wavelength above 300nm and at a pH greater than 7 in order to detect the formation of a compound of general formula (XIV) in which R_2 is H and X is O; or

b) measuring the fluorescence emission upon excitation at a selected wavelength in order to detect the formation of a compound of general formula (XIV) as defined in claim 19 in which R_2 is H and X is O.

37. A non-destructive method for quantifying the extent and/or rate of reaction of a linker-protein of general formula (XIV) as defined in claim 19 wherein R_2 is H and X is O, with an active moiety hydrazide, the process comprising measuring the intensity of the absorbance spectrum at a wavelength above 300nm and a pH less than 7.

38. A process for the preparation of a compound of general formula (XV) as defined in claim 22 in which:

R_2 is H and X is O;

the carrier has multiple residues Q;

a first selected percentage of the Q residues is derivatised with a first active moiety; and, optionally

further selected percentages of the Q residues are derivatised with further active moieties;

the process comprising:

a. reacting a compound of general formula (XIV) as defined in claim 19 in which R_2 is H and X is O with a first compound of general formula (XVI) as defined in claim 24 at a pH less than 7;

b. monitoring the progress of the reaction by measuring the intensity of the absorbance spectrum at a wavelength of above 300nm and stopping the reaction when the intensity of the absorbance spectrum reaches the first selected percentage of the known maximum intensity; and optionally

c. reacting the product of steps (a) and (b) with one or more further compounds of general formula (XVI), monitoring the progress of the reaction by measuring the intensity of the absorbance spectrum at a wavelength of above 300nm and stopping the reaction when the intensity of the absorbance spectrum reaches further selected percentages of the known maximum intensity.

39. A method for quantifying the extent and/or rate of release of an active moiety hydrazide from a compound of general formula (XV) as defined in claim 22 in which R_2 is H and X is O, the method comprising the measurement of the absorbance spectrum maximum at a wavelength above 300nm and at pH less than 7.

40. A compound as claimed in claim 22 or claim 25 wherein E or G is a labelling moiety.

41. A compound as claimed in claim 22 or claim 23 which is insoluble in aqueous solution.

42. A compound as claimed in claim 41 wherein E or G is a ligand which is specific for an analyte or a compound to be separated.

43. A compound as claimed in claim 42 which contains additional E or G groups derived from labelling molecules.

44. A method of separating a compound from a mixture, the method comprising contacting the mixture with a compound of general formula (XV) as defined in claim 22 in which E or G is a ligand which binds specifically to the compound to be separated and the carrier is a solid support

45. An assay method comprising contacting a mixture suspected of containing an analyte with a compound of general formula (XV) as described above in which E or G is a ligand which binds specifically to the analyte and the carrier is a solid support.

46. A wound dressing comprising a compound as claimed in claim 41 wherein the carrier is a functionalised polymer of the type commonly used in wound dressings and E or G is a peptide growth factor, a chemo-attractant protein, a ligand or an analogue of one of these.

47. A compound as claimed in claim 41 wherein the carrier is a functionalised polymer of the type commonly used in wound dressings and E or G is a peptide growth factor, a chemo-attractant protein, a ligand or an analogue of one of these for use in the treatment of wounds.

48. The use of compound as claimed in claim 41 wherein the carrier is a functionalised polymer of the type commonly used in wound dressings and E or G is a peptide growth factor, a chemo-attractant protein, a ligand or an analogue of one of these in the preparation of a dressing for use in the treatment of wounds.

49. Dialysis tubing comprising a compound as claimed in claim 41 wherein the carrier is a polymer suitable for use in dialysis tubing and E or G is heparin.

50. A compound as claimed in claim 41 wherein the carrier is a polymer suitable for use in dialysis tubing and E or G is heparin for use in the preparation of dialysis tubing.